SCIENTIFIC LETTER

Ischaemic preconditioning effect of prodromal angina pectoris is lost in patients with prior myocardial infarction

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Prodromal angina occurring shortly before the onset of acute myocardial infarction (MI) has a cardioprotective effect in patients with acute MI by the mechanism of ischaemic preconditioning.[1 2] However, it has been reported that several conditions, including aging and diabetes mellitus, may abolish the beneficial effect of prodromal angina.[3 4] Recent experimental studies have reported that the cardioprotective mechanism of preconditioning is impaired by post-MI left ventricular (LV) remodelling.[5] Patients with prior MI have an increased risk of developing acute MI. Once acute MI has occurred, the prognosis is worse than that for patients without prior MI. This study was undertaken to investigate the influence of prior MI on the effect of prodromal angina in patients with acute MI.

METHODS

This study enrolled 1076 patients with acute MI who underwent coronary angiography within 24 hours after the onset of chest pain. Acute MI was diagnosed by chest pain persisting longer than 30 minutes and concomitant ECG changes. Serum creatine kinase was measured every three hours. Peak creatine kinase concentration had to be more than twice the normal upper limit. Immediately after coronary angiography, reperfusion therapy was performed, if appropriate. Most (84%) of the patients underwent primary coronary angioplasty with (n = 584) or without coronary stents (n = 315). Contrast left ventriculography was performed before reperfusion therapy (n = 635) and at predischarge catheterisation (n = 656).

Prodromal angina was defined as typical chest pain episode(s) persisting < 30 minutes either at rest or on effort within 24 hours before the onset of acute MI. Data on whether the patients had prior MI based on their history or the presenting ECG were also collected and entered on to the case report form.

Data were statistically analysed with the χ^2 test and *t* test. In-hospital major adverse cardiac events (MACE) were defined as death, congestive heart failure, or repeat MI. Differences were considered significant at $p < 0.05$.

RESULTS

Prodromal angina was present in 428 patients (40%). Baseline characteristics did not differ significantly between patients with prodromal angina and patients without, except for more anterior MI in patients with prodromal angina. Acute end diastolic LV volume and LV ejection fraction (LVEF) did not differ significantly between patients with prodromal angina and patients without.

There were 137 patients (13%) with prior MI. Baseline characteristics did not differ significantly between patients with prior MI and patients without, except for more men and more multivessel disease among patients with prior MI. Patients with prior MI had a larger acute end diastolic LV volume (mean (SD) 127 (30) ml *v* 147 (38) ml, $p < 0.001$) and lower acute LVEF (53.1 (12.0)% *v* 50.0 (13.0)%, p = 0.05).

In patients without prior MI, prodromal angina was associated with significantly lower incidence of in-hospital mortality (3.4% *v* 7.0%, p = 0.02) and MACE (10.0% *v* 16.6%, p = 0.004) (fig 1). The mean (SD) concentration of peak creatine kinase was 2687 (2408) IU/l in patients with prodromal angina and 3100 (2389) IU/l in patients without prodromal angina (p = 0.01). Acute LVEF was not significantly different (53.6 (11.6)% *v* 52.8 (12.4)%, p = 0.44), but predischarge LVEF was significantly better in patients with prodromal angina than in patients without (58.3 (12.6)% *v* 55.7 (13.7)%, p = 0.02). The change in LVEF tended to be better in patients with prodromal angina than in patients without (5.7 (11.6)% *v* 3.7 (12.1)%, p = 0.07).

In the presence of prior MI, the incidence of in-hospital mortality (10.2% *v* 8.0%, p = 0.66) and MACE (22.5% *v* 20.5%, p = 0.78) did not differ significantly between patients with prodromal angina and in patients without (fig 1). The mean (SD) concentration of peak creatine kinase was 2522 (2304) IU/l in patients with prodromal angina and 2737 (2479) IU/l in patients without (p = 0.37). Acute LVEF (47.9 (13.9)% *v* 51.0 (12.4)%, p = 0.37), predischarge LVEF (46.5 (13.3)% *v* 53.0 (15.1)%, p = 0.06), and the change in LVEF (−0.5 (10.8)% *v* 1.2 (11.1)%, p % = 0.60) did not differ significantly between patients with prodromal angina and patients without.

DISCUSSION

Brief episodes of ischaemia have a cardioprotective effect against subsequent prolonged ischaemia. This phenomenon is termed ischaemic preconditioning.[1] The present study showed that prodromal angina was associated with a favourable outcome after acute MI in patients without prior MI, suggesting a cardioprotective effect of preconditioning. Although most previous experimental studies have investigated the effect of preconditioning in animal models in which ischaemia is imposed in the absence of other disease processes, most patients with acute MI have concomitant disease. Prior MI is associated with an increased risk of death after acute MI. Although prior MI was associated with more multivessel disease and impaired LV function before reperfusion therapy, which should increase mortality, prior MI has been shown to be an independent predictor for adverse outcome after acute MI even after these variables are adjusted.

Recently, Miki *et al*[5] reported that the cardioprotective mechanism of preconditioning is impaired in rabbits with prior MI and LV remodelling. The rabbits underwent a sham operation or coronary ligation to induce MI and LV remodelling. Two weeks later, the hearts were subjected to 30 minute ischaemia and two hour reperfusion. Although MI size was similar in sham operated and remodelled hearts, preconditioning with antecedent ischaemia protected sham operated but not remodelled hearts. Most previous clinical studies have investigated the cardioprotective effect of preconditioning in patients

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction

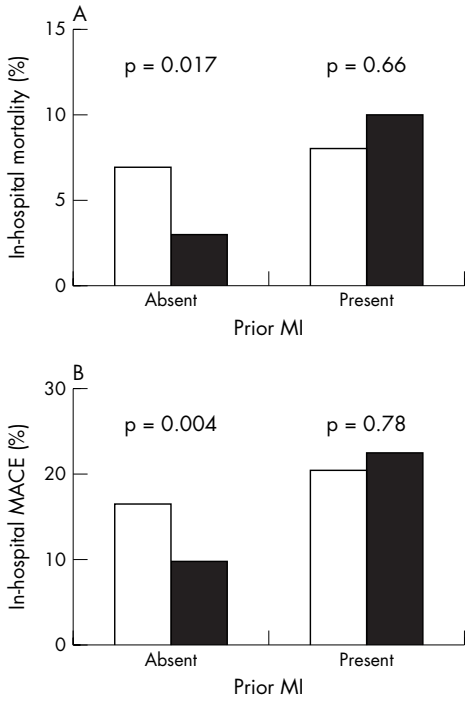

Figure 1 (A) In patients without prior myocardial infarction (MI), prodromal angina was associated with significantly lower in-hospital mortality. However, in the presence of prior MI, in-hospital mortality was not significantly different between patients with prodromal angina (black bar) and patients without prodromal angina (white bar). (B) In patients without prior MI, prodromal angina was associated with significantly lower incidence of major adverse cardiac events (MACE; death, congestive heart failure, or repeat MI). However, in the presence of prior MI, the incidence of MACE was not significantly different between patients with prodromal angina (black bar) and patients without prodromal angina (white bar).

without prior MI. In this study, the beneficial effect of prodromal angina was observed only in patients without prior MI, not in patients with prior MI. Patients with prior MI had a significantly larger acute end diastolic LV volume, suggesting the development of LV remodelling.

This study suffers from the limitations of all retrospective investigations. The modality of reperfusion therapy, however, was similar between patients with prodromal angina and patients without. The small sample size is another limitation of this study. However, it is noteworthy that, in the presence of prior MI, mortality and predischarge LVEF were not only significantly different but also tended to be worse in patients with prodromal angina.

In conclusion, prior MI abolished the cardioprotective effect of prodromal angina in patients with acute MI. Both impaired baseline LV function and loss of preconditioning may further worsen the outcome of acute MI in patients with prior MI.

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